

What is claimed is:

1. A modified neurotoxin comprising a neurotoxin including a structural modification, wherein the structural modification is effective to alter the biological persistence of the modified neurotoxin relative to an identical neurotoxin without the structural modification, and wherein the modified neurotoxin is structurally different from a naturally existing neurotoxin.
2. The modified neurotoxin of claim 1, which, other than the structural modification, does not include a leucine-based motif.
3. The modified neurotoxin of claim 2, wherein the structural modification includes a biological persistence enhancing component effective to enhance the biological persistence of the modified neurotoxin.
4. The modified neurotoxin of claim 3, wherein the biological persistence enhancing component comprises a leucine-based motif.
5. The modified neurotoxin of claim 3, wherein the enhanced biological persistence of the modified neurotoxin is at least in part due to an increased biological half-life of the modified neurotoxin.
6. The modified neurotoxin of claim 1, derived from an identical neurotoxin including a leucine-based motif.
7. The modified neurotoxin of claim 6, wherein the structural modification includes a leucine-based motif without one or more amino acids.
8. The modified neurotoxin of claim 7, wherein the biological persistence of the modified neurotoxin is reduced relative to an identical neurotoxin without the structural modification.

9. The modified neurotoxin of claim 8, wherein the reduced biological persistence of the modified neurotoxin is at least in part due to a decreased biological half-life of the modified neurotoxin.

5 10. A modified neurotoxin comprising a neurotoxin including a structural modification, wherein the neurotoxin comprises three amino acid sequence regions:

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- a) a first region effective as a neuronal binding moiety;
 - b) a second region effective to translocate the modified neurotoxin or a part thereof across an endosome membrane; and
 - c) a third region effective to inhibit neurotransmitter release when released into a cytoplasm of a target cell,
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16 wherein at least one of the first, the second and the third region is substantially derived from a Clostridial neurotoxin, the third region includes the structural modification, the modified neurotoxin is structurally different from a naturally existing neurotoxin, and the structural modification is

20 effective to alter the biological persistence of the modified neurotoxin relative to an identical neurotoxin without the structural modification.

25 11. The modified neurotoxin of claim 10, wherein the Clostridial neurotoxin is a member selected from a group consisting of botulinum toxin serotypes A, B, C, D, E, F, G, tetani toxin and mixtures thereof.

12. The modified neurotoxin of claim 10, wherein the third region is not derived from botulinum toxin serotype A.

13. The modified neurotoxin of claim 12, wherein the structural modification includes a biological persistence enhancing component effective to enhance the biological persistence of the modified neurotoxin.

5 14. The modified neurotoxin of claim 13, wherein the biological persistence enhancing component comprises a leucine-based motif.

15. The modified neurotoxin of claim 13, wherein the enhanced biological persistence of the modified neurotoxin is at least in part due to an increased biological half-life of the modified neurotoxin.

16. The modified neurotoxin of claim 14, wherein the leucine-based motif comprises an oligomer of seven amino acids, wherein the oligomer comprises a quintet of amino acids and a duplet of amino acids, wherein the
15 quintet of amino acids defines the amino terminal end of the leucine-based motif and the duplet of amino acids defines the carboxyl end of the leucine-based motif.

17. The modified neurotoxin of claim 16, wherein the quintet of amino
20 acids comprises at least one acidic amino acid, wherein the acidic amino acid is selected from a group consisting of a glutamate and an aspartate.

18. The modified neurotoxin of claim 16, wherein the quintet of amino
25 acids comprises at least one hydroxyl containing amino acid, wherein the hydroxyl containing amino acid is selected from a group consisting of a serine, a threonine and a tyrosine.

19. The modified neurotoxin of claim 18, wherein the hydroxyl containing amino acid can be phosphorylated.

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20. The modified neurotoxin of claim 16, wherein the duplet of amino acids comprises at least one hydrophobic amino acid, wherein the hydrophobic amino acid is selected from a group consisting of leucine, isoleucine, methionine, alanine, phenylalanine, tryptophan, valine and tyrosine.

21. The modified neurotoxin of claim 16, wherein the duplet of amino acids is member selected from a group consisting of leucine-leucine, leucine-isoleucine, isoleucine-leucine and isoleucine-isoleucine.

22. The modified neurotoxin of claim 14, wherein the leucine-based motif comprises an amino acid sequence phenylalanine-glutamate-phenylalanine-tyrosine-lycine-leucine-leucine (SEQ#1).

23. The modified neurotoxin of claim 22, wherein the structural modification includes fusing the phenylalanine-glutamate-phenylalanine-tyrosine-lycine-leucine-leucine sequence (SEQ#1) with the third region of the neurotoxin.

24. The modified neurotoxin of claim 23, wherein the phenylalanine-glutamate-phenylalanine-tyrosine-lycine-leucine-leucine sequence (SEQ#1) is fused with the carboxyl terminal of the third region of the neurotoxin.

25. The modified neurotoxin of claim 24, wherein the structural modification includes fusing the phenylalanine-glutamate-phenylalanine-tyrosine-lycine-leucine-leucine sequence (SEQ#1) with the carboxyl terminal of the third region of the neurotoxin, and wherein the first, the second and the third regions of the neurotoxin are derived from botulinum toxin serotype E.

26. The modified neurotoxin of claim 10, wherein the third region is derived from a botulinum toxin serotype A, which already contains a leucine-based motif.

5 27. The modified neurotoxin of claim 26, wherein the structural modification includes a leucine-based motif without one or more amino acids.

10 28. The modified neurotoxin of claim 27, wherein the biological persistence of the modified neurotoxin is reduced relative to an identical neurotoxin without the structural modification.

29. The modified neurotoxin of claim 28, wherein the reduced biological persistence is partly due to a decreased biological half-life of the neurotoxin.

15 30. The modified neurotoxin of claim 10, wherein at least one of the first, the second and the third region is recombinantly produced.

20 31. The modified neurotoxin of claim 10, wherein at least one of the first, the second and the third region is isolated from a naturally existing Clostridial neurotoxin.

25 32. A method for enhancing the biological persistence of a neurotoxin comprising the step of fusing a biological persistence enhancing component with the neurotoxin.

33. The method for enhancing the biological persistence of a neurotoxin of claim 32, wherein the biological persistence enhancing component is a leucine-based motif or a part thereof.

34. A method for reducing the biological persistence of a neurotoxin which contains a leucine-based motif comprising the step of deleting one or more amino acids from the leucine-based motif.

5 35. A method of treating a biological disorder, comprising the step of administering an effective dose of a modified neurotoxin to a mammal to treat the biological disorder, wherein the modified neurotoxin comprises a neurotoxin including a structural modification, and wherein the structural modification is effective to alter the biological persistence of the neurotoxin.

10 36. The method of treating a biological disorder of claim 35, wherein the neurotoxin is free from a leucine-based motif.

15 37. The method of treating a biological disorder of claim 36, wherein the structural modification includes a biological persistence enhancing component.

20 38. The method of treating a biological disorder of claim 37, wherein the biological persistence enhancing component comprises a leucine-based motif.

25 39. The method of treating a biological disorder of claim 35, wherein the biological disorder includes at least one of a neuromuscular disorder, an autonomic disorder and pain.

30 40. The method of treating a biological disorder of claim 39, wherein the treatment of the neuromuscular disorder comprises the step of locally administering an effective amount of the modified neurotoxin to a group of muscles.

41. The method of treating a biological disorder of claim 39, wherein the treatment of the autonomic disorder comprises the step of locally administering an effective amount of the modified neurotoxin to a gland.

5 42. The method of treating a biological disorder claim 39, wherein the treatment of pain comprises the step of administering an effective amount of the modified neurotoxin to the site of pain.

43. The method of treating a biological disorder of claim 39, wherein the
10 treatment of pain comprises the step of administering an effective amount of
the modified neurotoxin to the spinal cord.

Year	1990	1991	1992	1993	1994	1995	1996	1997	1998	1999	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017	2018	2019	2020	2021	2022	2023	2024	2025	2026	2027	2028	2029	2030	2031	2032	2033	2034	2035	2036	2037	2038	2039	2040	2041	2042	2043	2044	2045	2046	2047	2048	2049	2050	2051	2052	2053	2054	2055	2056	2057	2058	2059	2060	2061	2062	2063	2064	2065	2066	2067	2068	2069	2070	2071	2072	2073	2074	2075	2076	2077	2078	2079	2080	2081	2082	2083	2084	2085	2086	2087	2088	2089	2090	2091	2092	2093	2094	2095	2096	2097	2098	2099	2100
1990	1991	1992	1993	1994	1995	1996	1997	1998	1999	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017	2018	2019	2020	2021	2022	2023	2024	2025	2026	2027	2028	2029	2030	2031	2032	2033	2034	2035	2036	2037	2038	2039	2040	2041	2042	2043	2044	2045	2046	2047	2048	2049	2050	2051	2052	2053	2054	2055	2056	2057	2058	2059	2060	2061	2062	2063	2064	2065	2066	2067	2068	2069	2070	2071	2072	2073	2074	2075	2076	2077	2078	2079	2080	2081	2082	2083	2084	2085	2086	2087	2088	2089	2090	2091	2092	2093	2094	2095	2096	2097	2098	2099	2100	